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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/810,883 | 03/16/2001 | David Thomas | TNX98-08-01 | 2201 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/810,883 | THOMAS ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/1/05 has been entered. Applicant's amendment and response also filed on 3/1/05 has been entered. Claims 1-46 have been canceled and new claims 47-56 have been entered. Claims 47-56 are currently pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

### *Claim Rejections - 35 USC 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for methods of inhibiting the release of histamine

or TNF-alpha from mast cells comprising contacting the mast cells with a bispecific molecule capable of cross-linking the ITAM FcεRI and the ITIM FcγRIIB or FcεRII, does not reasonably provide enablement for said methods using bispecific antibodies which bind to any combination of the ITAMs and ITIMs recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The applicant's claims 53-57 recite methods of inhibiting the release of histamine or TNF-alpha from mast cells or basophils and methods of ameliorating allergic disease by administering a bispecific antibody of claim 47. Claim 47 recites a bispecific antibody comprising a first determinant that binds to an ITAM selected from a group consisting of BCR, FcεRI, FcγRI, FcγRIIA FcγRIIIA, and TCR, and a second determinant that binds to an ITIM selected from a group consisting of FcγRIIB, FcγRIII, and FcεRII.

The specification is primarily directed to the treatment of allergic disease by administering bispecific antibodies which cross-link an ITIM with an ITAM. The specification, while identifying a number of ITAMs, focuses primarily on the activity of the ITAM FcεRI, an IgE receptor present on mast cells and basophils whose activation results in the release of the inflammatory molecules histamine and TNF-alpha. The specification's working examples are exclusively directed to cross-linking FcεRI and an ITIM present on mast cells such as HM18, FcγRIIB, and FcεRII. The non-prophetic working examples demonstrate that indirect cross-linking of FcεRI and either FcγRIIB or FcεRII results in the inhibition of histamine and TNF-alpha release from mast cells in response to an antigen recognized by IgE bound to FcεRI. Specifically, the working examples utilize a combination of IgE anti-DNP and a chemically

conjugated anti-DNP/ anti-FcγRIIB bispecific antibody followed by DNP-HAS, or a combination of a IgE and a bispecific anti-IgE/anti- FcεRII antibody to cross-link FcεRI and either FcγRIIB or FcεRII. While none of the examples utilize a single bispecific antibody which specifically binds to an ITAM and an ITIM, the working examples do show an effect on mast cell degranulation and anaphylaxis by cross-linking FcεRI and FcγRIIB or FcεRII.

However, unlike FcεRI, a receptor specifically activated by IgE and expressed on effector cells associated with allergy such as mast cells and basophils, other ITAMs are not expressed on these cells types and were not reported in the literature to have any ability to modulate histamine or TNF-alpha release or expression. BCR and TCR, for instance, are the B cell receptor and T cell receptor respectively. BCR is only expressed on B cells, and TCR is only expressed on T cells. Neither B or T cells produce or release histamine. Further, the specification provides no guidance concerning the effects of cross-linking a BCR on a B cell or a TCR on a T cell with an ITIM present on a mast cell or basophil. The specification only appears to contemplate cross-linking an ITAM and an ITIM which are present on the same cell, and specifically a mast cell or basophil. This is because the ITIM functions to regulate and inhibit ITAM signaling intracellularly at the level of second and third messengers. Finally, although FcεRI is related to BCR and TCR by the presence of an ITAM domain in each of the molecules, the B cell receptor and T cell receptor and structurally and functionally different from FcεRI such that the skilled artisan would not be able to find a nexus between the applicant's working examples concerning the cross-linking of FcεRI and FcγRIIB or FcεRII on mast cells and the cross-linking of BCR or TCR with either FcγRIIB or FcεRII.

As such, due to the nature of the expression patterns of different ITAMs, the nature of the intracellular interactions between ITAM and ITIM signaling, the limitation of the guidance provided by the specification, including the working examples to the inhibition of mast cell activation by cross-linking FcεRI and FcγRIIB or FcεRII, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claim 47 recites, "wherein said ITIM is selected from the group consisting of FcγRIIB, FcγRIII, and FcεRII". However, FcγRIII can be either an ITAM or an ITIM. FcγRIIIA contains an ITAM domain whereas FcγRIIIB contains an ITIM domain. In regards to ITAMS, claim 47 lists FcγRIIIA. Therefore, the listing of FcγRIII as an ITIM is confusing in that it encompasses FcγRIIIA which is clearly an ITAM. As such the metes and bounds of the claim cannot be determined. If support for FcγRIIIB can be found in the specification, it is suggested that the claim be amended recite that the ITIM is FcγRIIIB. Otherwise, clarification is requested. Claim 48-56 depend on claim 47 and are therefore included in this rejection.

Claim 50 is further indefinite in that it lacks antecedent basis for the phrase, "the ITIM is FcγRII". Claim 47, from which claim 50 depends, recites that the ITIM is FcγRIIB. This rejection can be overcome by amending claim 50 to recite, "FcγRIIB".

Claim 55 is further indefinite in that it lacks antecedent basis for the phrase, "the bispecific antibody concentration". Claim 53, from which claim 55 depends, only recites administering the bispecific antibody of claim 47 and does not recite "bispecific antibody concentration". It is suggested that claim 55 be amended to recite, "wherein the bispecific antibody is administered at a concentration range from 0.1 to 1 ug/ml".

***Claim Rejections - 35 USC 102***

The rejection of canceled claims 29, 31, and 33-43 under 35 U.S.C. 102(a) as being anticipated by EP 0 861 891 A1. (1998), hereafter referred to as Daeron et al, is withdrawn in view of the cancellation of these claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 47-48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Vossebeld et al. (1995) J. Biol. Chem., Vol. 270, No. 18, 10671-10679. The applicant claims a

bispecific antibody comprising a first determinant that binds to an ITAM selected from a group which includes FcγRIIA and a second determinant that binds to an ITIM selected from a group which includes FcγRIII.

Vossebeld et al. teaches a bispecific antibody comprising a first determinant that binds to an ITAM selected from a group which includes FcγRIIA and a second determinant that binds to an ITIM selected from a group which includes FcγRIIIB in PBS, a physiological acceptable diluent (Vossebeld et al., abstract and page 10672, column 1). Thus, by teaching all the elements of the claims as written, Vossebeld et al. anticipates the instant invention as claimed.

***Claim Rejections - 35 USC 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 47-48, and 50-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katz et al. (1997) J. Immunol., Vol. 158, 5065-5070, in view of EP 0 861 891 A1. (1998), hereafter referred to as Daeron et al.. The applicant claims bispecific antibodies comprising a first determinant that binds to an ITAM selected from a group which includes FcεRI and a second determinant that binds to an ITAM selected from a group which includes FcγRIIB. The applicant further claims said antibodies wherein at least one determinant is an ScFv and methods

of administering said bispecific antibodies to inhibit histamine or TNF-alpha release from mast cells and to ameliorate allergic disease.

Katz et al. teaches that mast cells contain two inhibitory receptors containing ITIMs, gp49B1 and FcγRIIB, and that both inhibit mast cell activation and exocytosis of inflammatory molecules such as histamine following co-ligation with the ITAM FcεRI (Katz et al., page 5068). Katz et al. further teaches that while both ITIMs are inhibitory, each uses a different intracellular signaling pathway (Katz et al, page 5068).

While Katz et al. teaches that mast cells can be inhibited by co-ligation of the ITAM FcεRI and either the ITIM gp49B1 or the ITIM FcγRIIB, Katz et al. does not teach using a bispecific antibody to achieve coligation resulting in mast cell inhibition. Daeron et al. supplements Katz et al. by teaching bispecific molecules that can be used to coligate and ITAM and an ITIM. Like Katz et al., Daeron et al. teaches that both gp49B1 and FcγRIIB on mast cells contain ITIM domains and that coaggregation of these inhibitory molecules with the ITAM FcεRI results in mast cell inhibition (Daeron et al., page 9 and pages 13-14). Specifically, Daeron et al. teaches that co-aggregation of the ITAM FcεRI and the ITIM FcγRIIB results in the inhibition of extracellular calcium influx (Daeron et al., page 9). Daeron et al. further teaches that bispecific molecules useful for coaggregating an ITAM and an ITIM include bispecific antibodies that are capable of cross-linking a stimulatory ITAM receptor and a ITIM receptor (Daeron et al., pages 14-15, claims 1-15). The bispecific antibodies can further include at least one ScFv fragment (Daeron et al., claim 11). Daeron et al. also teaches that cross-linking of the ITAM and ITIM on a mast cell results in the modulation the release of inflammatory mediators and TNF-alpha (Daeron et al., page 14-15, especially claim 15). In addition, Daeron et al.

teaches pharmaceutical compositions comprising said bispecific antibodies and the use of the bispecific antibodies to treat allergy and to modulate TNF-α release (Daeron et al., pages 3-4).

While Daeron et al. particularly focuses on inhibition caused by crosslinking the ITAM FcεRI and the ITIM gp49B1, Daeron et al. clearly teaches, as noted above, that other ITIM containing molecules such as FcγRIIB can in fact exert inhibition on effector cell functions when crosslinked with an ITAM such as FcεRI (Daeron et al., page 9 and pages 13-14). Therefore, in view of the teachings of both Katz et al. and Daeron et al. that cross-linking the ITIM FcγRIIB and the ITAM FcεRI on mast cells results in the inhibition of mast cell activation, and particularly the inhibition of exocytosis of inflammatory molecules such as histamine and the release of TNF-alpha, and further in the view of the motivation to use bispecific antibodies to cross-link ITAM and ITIM on mast cells as taught by Daeron et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to make a bispecific antibody containing a first determinant that binds to the ITAM FcεRI and a second determinant that binds to the ITIM FcγRIIB and to use that bispecific antibody to cross-link FcεRI and FcγRIIB on mast cells. Further, based on the teachings of both Katz et al. and Daeron et al. that cross-linking FcεRI and FcγRIIB on mast cells results in inhibition of mast cell activation, the skilled artisan would have had a reasonable expectation of success in using a bispecific antibody capable of cross-linking FcεRI and FcγRIIB to inhibit the release of histamine and TNF-alpha from mast cells, thus ameliorating allergic disease.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER